

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-886**

**CHEMISTRY REVIEW(S)**

A. Chapman

JEC 28 1998

**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Original NDA Review of Chemistry, Manufacturing, and Controls

**NDA #:** 20-886

**CHEMISTRY REVIEW #:**

3

**REVIEW DATE:** December 17, 1998

**SUBMISSION TYPE**

Original  
Amendment (AC)  
Amendment (BC)  
Amendment (AZ)

**DOC. DATE**

May 26, 1998  
November 12, 1998  
November 17, 1998  
December 2, 1998

**CDER DATE**

May 27, 1998  
November 13, 1998  
November 18, 1998  
December 3, 1998

**ASSIGNED DATE**

June 3, 1998  
November 17, 1998  
November 18, 1998  
December 8, 1998

**NAME & ADDRESS OF APPLICANT:**

Ligand Pharmaceuticals Inc.  
10275 Science Center Drive  
San Diego, CA 92121-1117

**DRUG PRODUCT NAME:**

Proprietary:  
Nonproprietary/USAN:

Common Name:  
Code Name/Number:  
Chem. Type/Ther. Class:

Panretin® (Alitretinoin) Gel 0.1%  
Alitretinoin (This name was adopted by the USAN Council, see a copy dated 3/25/98 attached)  
9-cis-Retinoic acid  
ALRT1057, LGD1057, LG100057, AGN192013  
1P

**PHARMACOL. CATEGORY/INDICATION:**

**DOSAGE FORM:**

**STRENGTHS:**

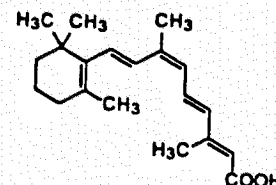
**ROUTE OF ADMINISTRATION:**

**DISPENSED:**

AIDS-related Kaposi's Sarcoma  
Topical Gel  
0.1%  
Topical Only  
☒ Rx ☐ OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA (M.F.), MOLECULAR WEIGHT (M.W.):**

CAS Name: 9-cis-Retinoic acid  
IUPAC Name: (2E, 4E, 6Z, 8E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid  
Common Name: 9-cis-Retinoic acid  
CAS Number: 5300-03-8  
Code Number: ALRT 1057, LGD 1057, LG100057, AGN 192013, NSC 659772  
M.F.: C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>  
M.W.: 300.44



**SUPPORTING DOCUMENTS:**

INDs: IND  
DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
		11/4/98	USP amber glass bottles (Soda Lime Amber Glass Containers)	Pending for review		
		11/5/98	Green Urea Screw Cap lined with	Pending for review		
		2/11/98	Collapsible aluminum tubes lined with	Pending for review		
		11/6/98	White screw cap with spike made from resin	Pending for review		

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

EER for

for

acceptable for

acceptable for

acceptable

Trademark "Panretin" consultation on 7/15/98, Acceptable with some concerns (E-mail dated 11/16/98)  
Micro consultation, not applicable

Environmental assessment, exemption is requested. Granted.

Stability data consultation, initiated on 10/1/98, completed on 11/4/98, 2<sup>nd</sup> request on 11/18/98, Pending  
Method validation will be initiated after satisfactory response to deficiencies regarding method validation.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

Responses submitted in the major amendment of 11/12/98 were found to be unsatisfactory.  
The NDA 20-886 is approvable from CMC standpoint, pending satisfactory responses to our comments noted in this review

/S/  
Sung K. Kim, Ph.D.,  
Review Chemist, HFD-150

cc:

Orig. NDA 20-886

HFD-150/Division File

HFD-150/CSO/AChapman

HFD-150/SKim

HFD-150/RWood

R/D Init. by: /S/ 12-28-98

filename: N20886.or2

**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
**Original NDA Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 20-886      **CHEMISTRY REVIEW #:** 2      **REVIEW DATE:** November 20, 1998

<u>SUBMISSION TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	May 26, 1998	May 27, 1998	June 3, 1998
Amendment (BL)	July 9, 1998	July 10, 1998	July 10, 1998
Amendment (BC)	August 28, 1998	August 31, 1998	September 3, 1998
Amendment (BL)	November 5, 1998	November 6, 1998	November 12, 1998

**NAME & ADDRESS OF APPLICANT:**

Ligand Pharmaceuticals Inc.  
 10275 Science Center Drive  
 San Diego, CA 92121-1117

**DRUG PRODUCT NAME:**

Proprietary:  
 Nonproprietary/USAN:

Common Name:  
 Code Name/Number:  
 Chem. Type/Ther. Class:

Panretin® (Alitretinoin) Gel 0.1%  
 Alitretinoin (This name was adopted by the USAN Council, see a copy dated 3/25/98 attached)  
 9-cis-Retinoic acid  
 ALRT1057, LGD1057, LG100057, AGN192013  
 1P

**PHARMACOL. CATEGORY/INDICATION:**

AIDS-related Kaposi's Sarcoma

**DOSAGE FORM:**

Topical Gel

**STRENGTHS:**

0.1%

**ROUTE OF ADMINISTRATION:**

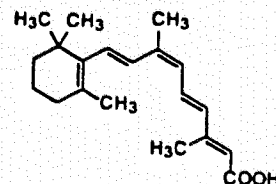
Topical Only

**DISPENSED:**

☒ Rx      ☐ OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):**

CAS Name: 9-cis-Retinoic acid  
 IUPAC Name: (2E, 4E, 6Z, 8E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid  
 Common Name: 9-cis-Retinoic acid  
 CAS Number: 5300-03-8  
 Code Number: ALRT 1057, LGD 1057, LG100057, AGN 192013, NSC 659772  
 M.F.: C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>  
 M.W.: 300.44



**SUPPORTING DOCUMENTS:**

INDs: IND

DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
		2/11/98	Collapsible aluminum tubes	Pending for review		

**RELATED DOCUMENTS (if applicable):**      N/A

**EER for**

acceptable for

**acceptable for**

## Pending for

**Environmental assessment, exemption is requested. Granted.**

Method validation: 11/18/98, Pending

**Method validation will be initiated after satisfactory response to deficiencies regarding method validation.**

CONCLUSIONS & RECOMMENDATIONS:

**CONCLUSIONS & RECOMMENDATIONS:**  
This NDA is approvable pending a satisfactory response to our comments forwarded on 10/27/98 and to labeling comments noted in this review.

Sung K. Kim, Ph.D.,  
Review Chemist, HFD-150

**cc:**

Orig. NDA 20-886

HFD-150/Division File

HFD-150/CSO/AC Chapman

**HFD-150/SKIm**

HFD-150/R Wood

R/D Init. by:

11-20-98

filename: N20886.or1

Ms. Chapman

OCT 26 1998

**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
**Original NDA Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 20-886

**CHEMISTRY REVIEW #:**

1

**REVIEW DATE:** October 26, 1998

<u>SUBMISSION TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	May 26, 1998	May 27, 1998	June 3, 1998
Amendment (NC)	June 4, 1998	June 5, 1998	June 11, 1998
Amendment (BC)	June 5, 1998	June 8, 1998	June 11, 1998
Amendment (NC)	June 16, 1998	June 17, 1998	June 24, 1998
Amendment (BC)	August 6, 1998	August 7, 1998	August 11, 1998
Amendment (BC)	September 23, 1998	September 24, 1998	(provide USAN Name) September 28, 1998 (provide stability update)

**NAME & ADDRESS OF APPLICANT:**

Ligand Pharmaceuticals Inc.  
10275 Science Center Drive  
San Diego, CA 92121-1117

**DRUG PRODUCT NAME:**

Proprietary: -  
Nonproprietary/USAN:

Panretin® (Alitretinoin) Gel 0.1%  
Alitretinoin (This name was adopted by the USAN Council, see a copy dated 3/25/98 attached)  
9-cis-Retinoic acid  
ALRT1057, LGD1057, LG100057, AGN192013  
IP

Common Name:  
Code Name/Number:  
Chem. Type/Ther. Class:

**PHARMACOL. CATEGORY/INDICATION:**

AIDS-related Kaposi's Sarcoma

**DOSAGE FORM:**

Topical Gel

**STRENGTHS:**

0.1%

**ROUTE OF ADMINISTRATION:**

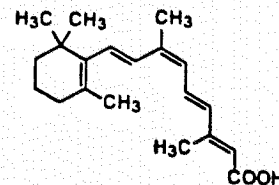
Topical Only

**DISPENSED:**

☒ Rx ☐ OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):**

CAS Name: 9-cis-Retinoic acid  
IUPAC Name: (2E, 4E, 6Z, 8E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid  
Common Name: 9-cis-Retinoic acid  
CAS Number: 5300-03-8  
Code Number: ALRT 1057, LGD 1057, LG100057, AGN 192013, NSC 659772  
M.F.: C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>  
M.W.: 300.44



**SUPPORTING DOCUMENTS:**

INDs: IND

DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
		2/11/98	Collapsible aluminum tubes	Pending for review		

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

*EER for*

**Pending**

*Trademark "Panretin" consultation on 7/15/98, Pending*

*Micro consultation, not applicable*

*Environmental assessment, exemption is requested. Granted.*

*Stability data consultation, initiated on 10/1/98, Pending*

*Method validation will be initiated after satisfactory response to deficiencies regarding method validation.*

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

CMC deficiencies were noted in this application. The deficiencies indicated in the draft letter should be forwarded to the applicant.

*TS/*

Sung K. Kim, Ph.D.,  
Review Chemist, HFD-150

cc:

Orig. NDA 20-886

HFD-150/Division File

HFD-150/CSO/ACHapman

HFD-150/SKim

HFD-150/RWood

R/D Init. by: */S/*

*10-26-98*

filename: N20886.org

1<sup>st</sup> Draft on 10/15/98

Final 10/26/98

**NDA 20-886 Review on Draft Tube Labeling submitted in the amendment of July 9, 1998**

**REVIEWER:** Sung K. Kim, Ph.D.

**DOCUMENT DATE:**

Original, May 26, 1998

Amendment, July 9, 1998

**REVIEW DATE:** July 23, 1998

**CDER DATE:**

May 27, 1998

July 10, 1998

**NAME AND ADDRESS OF APPLICANT:**

Ligand Pharmaceuticals Inc.  
10275 Science Center Drive  
San Diego, CA 92121-1117

**DRUG PRODUCT NAME:**

Proprietary:

Nonproprietary/USAN:

Code Name and Number:

CAS:

Chemical Name/Structure:

Panretin Topical Gel 0.1%

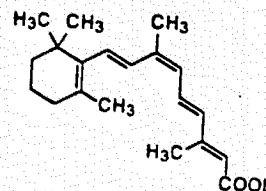
Alitretinoin

ALRT1057, LGD1057, LG100057,

AGN192013

5300-03-8

9-cis-retinoic acid



**DOSAGE FORM:**

**STRENGTH:**

**ROUTE OF ADMINISTRATION:**

**PHARMACOL. CATEGORY/INDICATION:**

Topical Gel

0.1%

Topical Only

AIDS-related Kaposi's Sarcoma

**RELATED IND:**

**COMMENTS:**

**CONCLUSION & RECOMMENDATIONS:**

The proposed tube labeling submitted in the amendment of 7/9/98 is deficient. We have a concern about the proposed trademark, "Panretin", because of the similarity of "Panretin" to "Pelretin" which has been approved as an USAN name should be forwarded to the applicant.

Comments

/s/

Review Chemist, HFD-150

cc:

Original NDA # 20-886

HFD-150/Div. File

HFD-150/CSO/ACHapman

HFD-150/SKim

HFD-150/RWood

R/D Init. by:

/s/

7-23-98